Nephrol Dial Transplant (2009) 24: 31–33
doi: 10.1093/ndt/gfn534
Advance Access publication 27 November 2008

NDT
Nephrology Dialysis Transplantation

Translational Nephrology

Low catechol-*O*-methyltransferase and 2-methoxyestradiol in preeclampsia: more than a unifying hypothesis*

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Keywords: angiogenesis; catecholestradiols; maternal syndrome; preeclampsia

Preeclampsia is a systemic disorder of pregnancy characterized by widespread maternal endothelial dysfunction. Clinical manifestations of preeclampsia include placental hypoxia, hypertension, proteinuria and fluid retention. The condition is common and affects over 5% of all pregnancies, thus remaining a leading cause of maternal and fetal morbidity and mortality worldwide [1]. Pregnancies complicated by preeclampsia are associated with greater risk and earlier onset of cardiovascular disease in both mother and infant [2,3]. Preeclampsia originates in the placenta, as it may occur only in the presence of placenta or a hydatiform mole and resolves dramatically postpartum after the delivery of the placenta. Generalized endothelial dysfunction resulting in vasoconstriction and end-organ ischaemia is attributed in all of the clinical aspects of the maternal syndrome in preeclampsia. Search for a unique circulating factor [4] resulted in an identification of multiple factors of endothelial dysfunction, activation and oxidative stress. A major breakthrough was achieved during the past five years by a series of experimental and clinical studies from Karumanchi and associates implicating that changes in circulating angiogenic factors play a decisive role in the pathogenesis of preeclampsia (reviewed in [5]). Increased expression of soluble fms-like tyrosine kinase 1 (sFlt1), a variant of the membrane-bound vascular endothelial growth factor (VEGF)-receptor 1 that consists of the extracellular ligand-binding domain, was associated with decreased placental growth factor (PIGF) and VEGF signalling and consecutive defective angiogenesis [6]. Soluble Flt1 acts as a natural antagonist of the circulating VEGF and increases from mid-gestation onwards, to reach the peak 5–8 weeks before the onset of the maternal syndrome [7]. Soluble endoglin, a circulating coreceptor that may inhibit transforming growth factor-β1 signalling, has properties similar to those of sFlt1 [8]. The excess sFlt1 contributed to various features of the maternal syndrome such as placental hypoxia with placental insufficiency or renal glomerular endotheliosis [5]. Thus, sFlt1 held a promise to fulfil the expectations of the 'mysterious circulating factor', as it linked placenta with various features of the maternal endothelial dysfunction. Another aspect of preeclampsia are immune-mediated mechanisms, as autoantibodies agonistic to the angiotensin II type 1 receptor (AT_1R) were found in the circulation of preeclamptic women [9]. The autoantibodies were later linked to oxidative stress, increased inflammation and shallow placentation (reviewed in [10]). Finally, introduction of IgG from preeclamptic women targeting AT_1R was found to increase the production of sFlt1 in the placenta [11]. Nonetheless, not all women with preeclampsia have increased sFlt1 and/or endoglin concentrations. Even fewer of them develop autoantibodies against AT_1R. Thus, there are several unanswered questions concerning the present view of preeclampsia pathogenesis, implicating that additional synergistic factors elaborated by the placenta may be capable of inducing a generalized endothelial dysfunction.

The recent work of K. Kanasaki and associates performed under the aegis of R. Kalluri and published recently in *Nature* in June this year seems to provide a foundation for the unifying hypothesis on the pathogenesis of preeclampsia [12]. The authors demonstrated that pregnant mice deficient in catechol-*O*-methyltransferase (COMT) develop multiple functional and structural features of preeclampsia-like phenotype. COMT-deficient mice delivered preterm with higher wastage of fetuses and showed a higher blood pressure and a higher urinary albumin excretion in comparison with wild-type mice [12]. The arteriopathy of the placenta in the COMT-deficient mice resembled human decidual vascular lesion, and glomerular endotheliosis was also present. Levels of hypoxia-inducible factor-1α (HIF-1α) protein were higher in the placenta and the sFlt1 plasma concentrations were significantly higher in pregnant COMT-deficient mice compared to controls. Administration of 2-methoxyestradiol (2-ME) rescued the COMT-deficient mice from the preeclampsia-like syndrome without toxicity. Moreover, 2-ME ameliorated

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*Comment on Kanasaki K, Palmsten K, Kalluri R *et al.* Deficiency in catechol-*O*-methyltransferase and 2-methoxyoestradiol is associated with pre-eclampsia. *Nature* 2008; 453: 1117–1121.

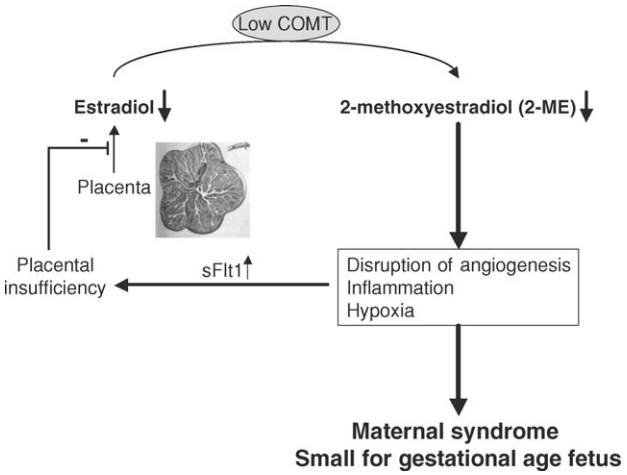

Fig. 1. Scheme depicts pathophysiologic consequences and clinical manifestations resulting from diminished 2-ME synthesis induced by pharmacologically or genetically induced low- or lack of COMT activity: disruption of angiogenesis and consecutive hypoxia in parallel to local inflammatory processes are mediated by sFlt-1 and thereby connect placental insufficiency with consecutive maternal syndrome and fetal growth retardation.

placental hypoxia by inhibition of HIF-1α expression and precluded sFlt1 elevation [12]. Schematic view of how COMT–2-ME interactions contribute to the pathogenesis of maternal syndrome in preeclampsia is provided in Figure 1. In parallel, 2-ME was elevated during the third trimester of normal human pregnancies, while in contrast, the levels of COMT and 2-ME were lower in women with severe preeclampsia. These observations were confirmed by the pharmacologic study, in which the inhibition of COMT induced manifestations of preeclampsia in normal pregnant mice, resembling the COMT-deficient pregnancy phenotype [12]. Administration of 2-ME prevented the increase in blood pressure and occurrence of proteinuria. The protective effect of 2-ME was again attributed to resolution of the hypoxia-induced disruption of the angiogenic balance. Finally, normal pregnant mice developed preeclampsia when given an inhibitor of a precursor of the 2-ME protein. Taken together, 2-ME, generated in the placenta by COMT, not only protects against generalized endothelial dysfunction, but also suppresses sFlt1. Thus, the missing pieces in the preeclampsia puzzle connecting angiogenic disequilibrium with generalized endothelial dysfunction, and the placental insufficiency seem to be found.

Methoxyestradiols are major endogenous metabolites of estradiol [13] with no affinity to oestrogen receptors [14]. Estradiol is metabolized to hydroxyestradiol by cytochorme P450 enzymes and hydroxyestradiol is methylated by COMT to 2-ME [14]. Normally, catecholamines do not interfere with the metabolism of estradiol to 2-ME, yet production of 2-ME may be seriously compromised in cardiovascular pathologies associated with an increased release of catecholamines. Sympathetic activation with increased concentrations of circulating catecholamines and generalized vascular constriction are present in preeclampsia [15]. Catecholamines compete with catecholestradiols for COMT-induced methylation, which results in an impaired metabolization towards 2-ME. There are multiple implications of these findings that may affect clinical management of preeclampsia, in particular, in terms of more precise assessment of risk pregnancies. Thus, 2-ME may have importance as a plasma and urine diagnostic marker of preeclampsia but may also serve as a therapeutic supplement to prevent or treat preeclampsia, as well as some other cardiovascular or renal conditions. While linking COMT to 2-ME provides greatly advances our knowledge in terms of the pathogenesis of preeclampsia, the protective role of 2-ME in cardiovascular and renal pathologies is not completely new. It has been shown that 2-ME acts inhibitorily on proliferation, migration and growth of vascular smooth muscle, endothelial cells and mesangial cells [14,16,17]. Compared to men and postmenopausal women, premenopausal women are relatively protected against various cardiovascular and renal pathologies. Better definition for COMT- and 2-ME-related mechanisms should help us to understand sex-specific differences in renal disease pathogenesis and progression beyond oestrogen-receptor-associated actions. The activity of COMT is controlled by an autosomal dominant inherited functional polymorphism that encodes for the low, high and intermediate activity of the enzyme [18]. Genetically determined COMT activity is not only critically involved in the regulation of affective mood and pain perception [19], but also influences outcomes in patients with ischaemic heart disease [20], implicating that the carriers of the low-activity COMT genotype seem to be susceptible to various stressors. The stage for the COMT–2-ME couple is set in the renal and cardiovascular arena, and we should eagerly await new contributions.

Conflict of interest statement. None declared.

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Received for publication: 20.8.08
Accepted in revised form: 1.9.08